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EDITORIAL

Noninvasive neuromonitoring in acute brain injured patients

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While neurological assessment is a crucial element in the management of acute brain-injured (ABI) patients, conducting a comprehensive clinical evaluation may not be feasible during the acute phase, especially when patients require sedation. Invasive methods are considered the gold standard for neuromonitoring when indications are met [1]. However, in recent years, several noninvasive monitoring (NIM) techniques emerged with the ability to identify and follow subtle changes in intracranial physiology. With diverse physics principles, strengths, limitations and levels of evidence, these techniques demonstrated potential to play a role on the follow-up of neurocritical patients. In this manuscript, we briefly summarize some of the main NIM tools currently used in neurocritical care (Fig. 1).

Noninvasive monitoring of brain hemodynamics

Brain ultrasound (BUS) is being progressively used in the neurocritical care settings as a bedside repeatable and safe tool able to assess cerebral hemodynamics [1]. Transcranial color-duplex sonography (TCCD) combines Doppler pulse wave technology with B-mode, providing a direct visualization of brain anatomy and pathological events, such as intracerebral hemorrhage, masses, hydrocephalus, midline shift. TCCD can help to obtain direct anatomical information that may trigger indications for repeating imaging, or detect emerging brain catastrophes, such as bleeding—as well as provide a direct visualization and identification of the major intracranial vessels and their blood flow velocities.

Through the waveform analysis of the flow velocities on TCCD, important information can be obtained regarding cerebral blood flow (CBF), cerebrovascular autoregulatory status and estimation of cerebral perfusion pressure and noninvasive intracranial pressure (ICP—based mainly on the pulsatility index > 1.3 and diastolic flow velocity < 20 cm/s) [1, 2]. Slow velocities are indicators of intravascular blood volume reduction, whereas hyperdynamic blood transit may be due to systemic (hyperemia, septic status) or central causes (vasospasm, stenosis) [3]. Moreover, BUS is used to help in the diagnosis of different conditions in the intensive care unit (ICU), such as brain death, embolic phenomena and right-left vascular shunt.

Noninvasive monitoring of brain electrical activity

Guidelines recommend to consider intermittent or continuous electroencephalogram (EEG) monitoring for comatose patients [4]. Monitoring of electrical activity with EEG is very useful in detecting seizures and starting treatment, as well as escalating antiepileptic strategy in a timely line [5]. Seizures in comatose patients are highly correlated with structural brain damage but also with brain dysfunction, from epileptiform discharges (ED) up to non-convulsive status epilepticus [6]. Computational analysis also known as quantitative EEG (QEEG), involves the recording of digital EEG signals that are processed, transformed and analyzed using complex mathematical algorithms, obtaining specific frequency bands which allow a rapid and bedside screening and display of a large amounts of digitally recorded EEGs [7]. QEEG is able to detect seizures especially in non-convulsive status, but also monitor for ischemia, bleeding, hydrocephalus, brain swelling or herniation and to assess sedation depth [5, 8]. In addition, QEEG can help in the recognition of malignant patterns which are associated with poor outcomes [7].

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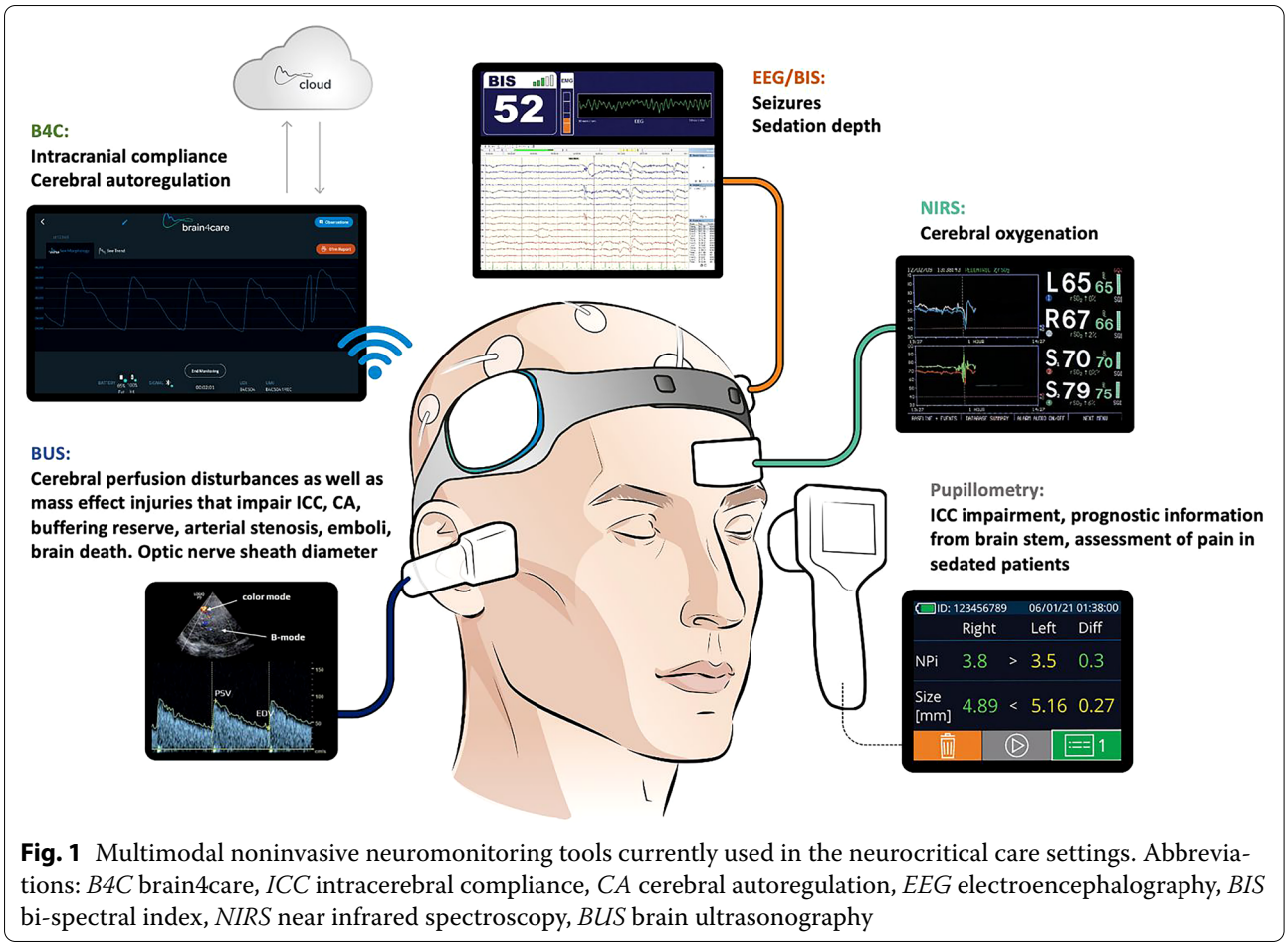

Fig. 1 Multimodal noninvasive neuromonitoring tools currently used in the neurocritical care settings. Abbreviations: *B4C* brain4care, *ICC* intracerebral compliance, *CA* cerebral autoregulation, *EEG* electroencephalography, *BIS* bi-spectral index, *NIRS* near infrared spectroscopy, *BUS* brain ultrasonography

Noninvasive monitoring of brain function

Automated pupillometer is a portable device which measures pupil size at baseline and changes after delivering a 3 seconds flash of visible light, and optimizes the accuracy of the pupillary examination, which is well established as a fundamental aspect of the neurological exam. It allows objective, quantitative, and reliably repeatable assessment of the brainstem function, by means of a variety of parameters including pupil size, latency, constriction and dilation velocities [7]; indeed, it is a validated monitor of brain function, by its graded assessment of central reflex pathways, that are indicative of more global brain pathophysiological issues (e.g., increased ICP, anoxic damage). The neurological pupil index (NPi; NeurOptics), an automated algorithm which incorporates multiple pupillometry parameters, has shown to be a good prognostic tool in post-cardiac arrest encephalopathy and in neurocritical care patients, and to present a correlation with high ICP when abnormal (values 0–3) [9, 10].

Noninvasive monitoring of brain mechanical properties

The adequate balance of intracranial volumes (intracranial compliance—ICC) is fundamental to ensure a proper cerebral blood perfusion. In this regard, the skull microdynamics sensor (B4C) is an emerging technique based on nanometric resolution of the pulsatile cranial elastic movements within each heartbeat [11, 12]. This system exports all acquired signals with privacy to a cloud analytics, which returns to the operator the processed ICP surrogate waveforms in real time. The numerical metrics currently provided are the P2/P1 ratio and the time-to-peak, which are used to assess ICC deterioration [11]. Studies in neurocritical patients validated B4C biomarkers against the invasive techniques, whereas clinical exploratory trials have indicated a potential utilization of this system in situations when ICC can be compromised for systemic factors (i.e. acute respiratory distress syndrome [13]). Moreover, some trials point out also to the possibility of NIM synergism and diagnostic power

enhancement combining different techniques such as BUS and B4C [13, 14]. In particular, BUS also allows the estimation of the optic nerve sheath diameter. As the optic nerve is surrounded by the meninges, its diameter increases when the pressure in the cerebral spinal fluid increases, being values > 5.8 mm associated with increased ICP [1]. This suggests a combined potential use of these tools with invasive ICP to help in the decision of escalating and deescalating treatment for ICP.

Noninvasive monitoring of brain oxygenation

Near-infrared spectroscopy (NIRS) measures tissue hemoglobin oxygen saturation (rSO_2) [15]. NIRS is composed by two sensors positioned over the frontal lobes with light sources, providing rSO_2 as a global indicator of cerebral oxygenation. It reflects the balance between oxygen consumption and delivery and derives from combined arterial, capillary, and venous blood. NIRS has been widely applied to identify episodes of cerebral desaturation in different settings, in particular in non-ABI patients, suggesting that $rSO_2 < 50\%$ or drop > 10–20% from basal are associated with neurological complications [16]. However, this technique has important methodological and technical issues, in particular the risk of contamination by extracranial signals; current recommendation suggest the use of invasive (brain tissue oxygenation) for the measurement of cerebral oxygenation [17], and the use of NIRS in ABI is limited.

Applications and take-home message

The arsenal of NIM tools has grown, allowing physicians to enhance their diagnostic ability.

NIM techniques have some advantages, as these are safe, relatively low cost, bedside available and repeatable. However, these present also some important limitations especially regarding accuracy, the need of training in some cases, and therefore cannot substitute invasive methods such as invasive ICP or oxygenation and are not currently routinely employed in clinical practice. Dedicated prospective trials are needed to determine the optimal combinations and their interactions with invasive monitoring, and to assess their effect on outcomes. Emerging evidence suggest that noninvasive methods can help in the understanding of cerebral physiology, and therefore can be employed together with invasive tools or when invasive techniques are not available or contraindicated (such as in coagulopathy) or in the screening of patients with borderline indications for invasive methods in the decision to proceed with invasive strategies or to help in the prognosis of patients. A multimodal noninvasive approach can improve the accuracy in estimating ICP and in the prediction of outcomes [18].

Each NIM presents strengths and weakness; the choice of the NIM to be used depends on the local availability, operator's training and the clinical question (brain mechanics properties, electrical activity, hemodynamics); finally, their use should be included in the context of a multimodal approach including neuroimaging and clinical factors.

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Data availability
Not applicable.

Declarations

Conflicts of interest
SB serves as a scientific advisor for brain4care. CR received fees for Speaker from Edwards, Masimo, RC holds an Integra Endowed Professor of Neurotrauma.

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